ORIGINAL ARTICLE

Intensive LDL Cholesterol Targeting in Atherosclerotic Cardiovascular Disease

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ABSTRACT

BACKGROUND

Despite guideline recommendations, evidence from randomized trials evaluating the appropriate low-density lipoprotein (LDL) cholesterol target for secondary prevention in patients with atherosclerotic cardiovascular disease remains limited.

METHODS

In this open-label superiority trial conducted in South Korea, we randomly assigned patients with atherosclerotic cardiovascular disease in a 1:1 ratio to a target LDL cholesterol level of less than 55 mg per deciliter (1.4 mmol per liter) (intensive-targeting group) or less than 70 mg per deciliter (1.8 mmol per liter) (conventional-targeting group). The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina at 3 years. Safety was also assessed.

RESULTS

Of 3048 patients who underwent randomization, 1526 were assigned to the intensive-targeting group and 1522 to the conventional-targeting group. The median follow-up was 3.0 years. The median LDL cholesterol level during the trial was 56 mg per deciliter (1.4 mmol per liter) in the intensive-targeting group and 66 mg per deciliter (1.7 mmol per liter) in the conventional-targeting group. A primary end-point event occurred in 100 patients (Kaplan–Meier estimate of cumulative incidence, 6.6%) in the intensive-targeting group and in 147 patients (Kaplan–Meier estimate of cumulative incidence, 9.7%) in the conventional-targeting group (hazard ratio, 0.67; 95% confidence interval, 0.52 to 0.86; P=0.002). The incidence of prespecified safety end points was similar in the two trial groups, except for a lower incidence of creatinine elevation in the intensive-targeting group.

CONCLUSIONS

Among patients with atherosclerotic cardiovascular disease, targeting an LDL cholesterol level of less than 55 mg per deciliter resulted in a lower risk of cardiovascular events at 3 years than targeting a level of less than 70 mg per deciliter. (Funded by the Cardiovascular Research Center and Yuhan; Ez-PAVE ClinicalTrials.gov number, NCT04626973.)

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*A complete list of the Ez-PAVE investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Patients with atherosclerotic cardiovascular disease are at high risk or very high risk for future cardiovascular events.[1-4] Low-density lipoprotein (LDL) cholesterol is the primary target for management of dyslipidemia, and intensive lowering of LDL cholesterol levels is recommended in these patients.[1-4] These recommendations are based on data from previous randomized trials showing that high-intensity statins or the addition of ezetimibe or proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors to statins reduces LDL cholesterol levels and the risk of cardiovascular events.[5-10] However, these trials aimed primarily to evaluate the effects of intensive lipid-lowering drugs rather than to determine specific targets for LDL cholesterol levels.[5-10]

In the past several years, guidelines for dyslipidemia have lowered the recommended LDL cholesterol target for patients with atherosclerotic cardiovascular disease from less than 70 mg per deciliter (1.8 mmol per liter) to less than 55 mg per deciliter (1.4 mmol per liter).[1-4] However, evidence supporting this stricter target remains limited, and randomized trials evaluating the cardiovascular benefits of targeting an LDL cholesterol level of less than 55 mg per deciliter rather than less than 70 mg per deciliter in patients with atherosclerotic cardiovascular disease are lacking. Given this uncertainty, a substantial gap exists between the guideline-recommended LDL cholesterol target and the implementation of this recommendation in clinical practice.[11,12] Therefore, the Ez-PAVE trial (Effects of Ezetimibe Combination Therapy for Patients with Atherosclerotic Cardiovascular Disease — Randomized Comparison of LDL Cholesterol Targeting <70 mg per Deciliter vs. <55 mg per Deciliter) was designed to investigate whether targeting an LDL cholesterol level of less than 55 mg per deciliter is superior to targeting a level of less than 70 mg per deciliter for preventing recurrent major cardiovascular events in patients with atherosclerotic cardiovascular disease.

Methods

Trial Design and Oversight

We conducted this investigator-initiated, multicenter, open-label, randomized superiority trial in South Korea. All the participating centers and trial personnel are listed in the Supplementary Appendix (available with the full text of this article at NEJM.org). The trial protocol (available at NEJM.org) and subsequent amendments were approved by the institutional review board or ethics committee at each participating site.

The trial was funded by an investigator-initiated grant from the Cardiovascular Research Center (South Korea) under a contract with Yuhan. The funders had no role in the design of the trial, in the collection or analysis of the data, in the interpretation of the trial results, or in the writing of the manuscript. Data were reviewed by an independent data and safety monitoring board at regular intervals. The first, second, and last authors had unrestricted access to the trial databases, participated in the analysis and interpretation of the data, and wrote the first and subsequent drafts of the manuscript. All the authors made the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Trial Population

Patients were eligible to participate in the trial if they were 19 to 80 years of age and had documented atherosclerotic cardiovascular disease, which was defined as the previous occurrence or presence of at least one of the following: previous acute coronary syndrome (myocardial infarction or unstable angina), stable angina with imaging or functional studies, coronary revascularization or other arterial revascularization, stroke or transient ischemic attack, or peripheral artery disease.[2-4] A key exclusion criterion was an LDL cholesterol level of less than 70 mg per deciliter without statin therapy. Full eligibility criteria are provided in the Supplementary Appendix. Written informed consent was obtained from all the patients before randomization.

Randomization and Treatment

Eligible patients were randomly assigned in a 1:1 ratio to a target LDL cholesterol level of less than 55 mg per deciliter (intensive-targeting group) or less than 70 mg per deciliter (conventional-targeting group). A Web response system with permuted-block randomization (with mixed blocks of 4 or 6) was used at each participating site for randomization, with stratification according to previous acute coronary syndrome (yes or no), the presence of diabetes (yes or no), and baseline

LDL cholesterol level (<100 mg per deciliter [<2.6 mmol per liter] or ≥100 mg per deciliter). Furthermore, the patients in each group underwent a second random assignment in a 1:1 ratio to one of two treatment regimens: statin monotherapy or combination therapy with statin plus ezetimibe. The patients assigned to the statin-monotherapy group were further randomly assigned in a 1:1 ratio to receive one of two statin types: rosuvastatin or atorvastatin. The patients assigned to the combination-therapy group received rosuvastatin together with ezetimibe (additional details are provided in the Supplementary Appendix). These additional randomizations were incorporated to enable timely achievement of the target LDL cholesterol levels and to balance the distribution of statin types while maintaining the primary comparison between LDL cholesterol targets.

Investigators were provided with basic instructions to guide initial and follow-up therapy for achieving the assigned target LDL cholesterol level (see the Supplementary Appendix). The intensity of trial drugs was classified according to the guidelines of the American College of Cardiology and the American Heart Association, as well as data from previous trials of ezetimibe.[3,8,13] After randomization, the patients received LDL cholesterol–lowering therapy according to their assigned treatment group and baseline LDL cholesterol levels. During follow-up, adjustment of medications was performed as needed to achieve target LDL cholesterol levels. Increasing the statin dose and adding ezetimibe were recommended before consideration of PCSK9 inhibitors. Although investigators were encouraged to follow these basic instructions, the primary aim was to achieve target LDL cholesterol levels effectively and safely; therefore, treatment decisions, including adjustment of statin doses and the addition of ezetimibe or PCSK9 inhibitors, were left to the discretion of the treating physicians in both trial groups, with detailed documentation of the rationale.

Follow-up assessments were performed at baseline, at 1 month, and at 1, 2, and 3 years after randomization. At each visit, general health status, use of medication, occurrence of end-point events or adverse events, and lipid profiles, including LDL cholesterol levels, were assessed. Laboratory assessments for safety were performed at predefined time points (additional information is provided in the protocol). Survival status was cross-validated with the Korean National Health Insurance database.

END POINTS

The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina at 3 years after randomization. Secondary end points included efficacy and safety measures. Efficacy end points included the individual components of the primary end point, as well as additional prespecified composite end points, including a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Safety end points included new-onset diabetes (among patients without diabetes at baseline), worsening of glycemic control (among patients with diabetes at baseline), statin-associated muscle symptoms leading to changes in therapy dose or regimen, diagnosis of cancer, cataract surgery, and elevation of the aminotransferase, creatinine, or creatine kinase level. The full list of trial end points and their prespecified definitions is provided in the Supplementary Appendix. An independent clinical-events committee whose members were unaware of trial-group assignments and LDL cholesterol levels adjudicated all cardiovascular events, cases of new-onset diabetes, and worsening of glycemic control. Other safety end points were evaluated through the collection of data on adverse events and laboratory assessments.

STATISTICAL ANALYSIS

The primary objective of the trial was to evaluate the hypothesis that intensive targeting of LDL cholesterol levels would be superior to conventional targeting with respect to the primary end point. We estimated that an enrollment of 3048 patients would provide the trial with 80% power, at a two-sided alpha level of 0.05, to detect a 24.75% lower relative risk of a primary end-point event at 3 years in the intensive-targeting group than in the conventional-targeting group, under the assumption of a 3-year incidence of 15% in the conventional-targeting group and a 15% loss to follow-up. These estimates were based on data from previous studies and assumptions about cumulative exposure to LDL cholesterol, as described in the Supplementary Appendix.[6,7,14,15]

All primary analyses were performed in the

intention-to-treat population, which included all the patients who had undergone randomization. The cumulative incidence of primary end-point events at 3 years was estimated with the Kaplan–Meier method and compared with the use of a log-rank test. Hazard ratios and 95% confidence intervals were estimated with a Cox proportional-hazards regression model. We tested and confirmed the proportional-hazards assumption for the primary end point by calculating the Schoenfeld residuals (P=0.92). A per-protocol analysis that excluded patients with major protocol deviations (discontinuation of LDL cholesterol–lowering therapy or reduction of therapy intensity despite not reaching target levels, unless discontinuation or reduction was prompted by adverse events) was performed for the primary end point. Competing-risk sensitivity analyses for the primary and secondary end points were performed with the Fine–Gray subdistribution hazard model.[16] Subgroup analyses for the primary end point were performed for prespecified subgroups stratified according to age, sex, body-mass index, previous acute coronary syndrome, coronary or other arterial revascularization, stroke or transient ischemic attack, peripheral artery disease, hypertension, diabetes, chronic kidney disease, and baseline LDL cholesterol level.

Data were collected and analyzed according to the predefined statistical analysis plan, available with the protocol. No interim analyses were conducted, and no imputation was performed to infer missing values. The 95% confidence intervals for secondary end points or for subgroups were not adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All the statistical analyses were performed with SAS software, version 9.4 (SAS Institute), and R software, version 4.5.0 (R Foundation).

RESULTS

PATIENTS, TREATMENTS, AND FOLLOW-UP

From January 2021 through July 2022, a total of 3048 patients underwent randomization at 17 sites in South Korea; 1526 were assigned to the intensive-targeting group and 1522 to the conventional-targeting group (Figs. S1 and S2 in the Supplementary Appendix). The characteristics of the patients at baseline appeared to be balanced between the two trial groups (Table 1). The mean (±SD) age of the patients was 64.4±9.0 years, 638 patients (20.9%) were women, and the median LDL cholesterol level was 76 mg per deciliter (interquartile range, 61 to 96) (2.0 mmol per liter [interquartile range, 1.6 to 2.5]). Of the patients who underwent randomization, 1694 (55.6%) had previous acute coronary syndrome, 1474 (48.4%) had stable angina with imaging or functional studies, 2049 (67.2%) had had coronary revascularization or other arterial revascularization, 117 (3.8%) had had a stroke or transient ischemic attack, and 266 (8.7%) had peripheral artery disease.

At 1 month, the percentage of patients receiving high-intensity statins was 53.5% in the intensive-targeting group and 35.9% in the conventional-targeting group; at 1, 2, and 3 years, the percentages were 54.0%, 50.8%, and 48.4%, respectively, in the intensive-targeting group and 34.3%, 32.7%, and 32.3%, respectively, in the conventional-targeting group. The percentage of patients receiving ezetimibe at 1 month was 49.7% in the intensive-targeting group and 50.0% in the conventional-targeting group; the percentages at 1, 2, and 3 years were 56.0%, 61.2%, and 66.6%, respectively, in the intensive-targeting group and 53.1%, 52.5%, and 56.7% in the conventional-targeting group. PCSK9 inhibitors were in use by 0.2% of the patients in the intensive-targeting group at 1 month and by 0.8%, 1.4%, and 2.3% at 1, 2, and 3 years, respectively, and by 0.1% of the patients in the conventional-targeting group at 1 month and by 0.5%, 0.5%, and 0.9% at 1, 2, and 3 years (Table S1). Details of the strategies for LDL cholesterol–lowering therapy according to the intensity of the statin and the use of ezetimibe, as well as data on the use of nonassigned therapy regimens and other cardiovascular drugs, are provided in Figures S3 and S4 and Table S2. During a median follow-up of 3.0 years (interquartile range, 3.0 to 3.0), a total of 110 patients (3.6%; 62 in the intensive-targeting group and 48 in the conventional-targeting group) discontinued LDL cholesterol–lowering therapy or underwent a downward adjustment in the intensity of therapy despite not reaching target LDL cholesterol levels, with the primary reason being an adverse event in 85 patients (2.8%; 50 in the intensive-targeting group and 35 in the conventional-targeting group) (Table S3). In addition, 14 patients (0.5%) withdrew consent, and 5 patients (0.2%) were lost to follow-up.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intensive Targeting (N=1526)	Conventional Targeting (N=1522)
Age — yr	64.2±9.1	64.6±9.0
Male sex — no. (%)	1204 (78.9)	1206 (79.2)
Median height (IQR) — cm	167 (160–171)	166 (160–170)
Median weight (IQR) — kg	68 (62–75)	68 (61–75)
Median body-mass index (IQR)†	24.9 (23.0–26.8)	24.7 (23.1–26.8)
Type of atherosclerotic cardiovascular disease — no. (%)‡		
Previous acute coronary syndrome	827 (54.2)	867 (57.0)
Myocardial infarction	460 (30.1)	481 (31.6)
Unstable angina	367 (24.0)	386 (25.4)
Stable angina with imaging or functional studies§	744 (48.8)	730 (48.0)
Coronary or other arterial revascularization	1015 (66.5)	1034 (67.9)
Percutaneous coronary intervention	884 (57.9)	900 (59.1)
Coronary-artery bypass grafting	58 (3.8)	71 (4.7)
Other arterial revascularization	88 (5.8)	82 (5.4)
Stroke or transient ischemic attack	57 (3.7)	60 (3.9)
Peripheral artery disease	132 (8.7)	134 (8.8)
Hypertension — no. (%)	1136 (74.4)	1103 (72.5)
Diabetes — no. (%)	605 (39.6)	602 (39.6)
Chronic kidney disease — no. (%)¶	91 (6.0)	87 (5.7)
Current smoker — no. (%)	348 (22.8)	388 (25.5)
Median lipid level (IQR) — mg/dl		
LDL cholesterol	77 (60–96)	75 (61–97)
HDL cholesterol	46 (40–55)	47 (39–54)
Total cholesterol	143 (123–167)	143 (123–167)
Triglycerides	117 (87–159)	115 (83–163)
Lipid-lowering therapy — no. (%)		
Statin‖		
High intensity	352 (23.1)	349 (22.9)
Moderate intensity	1036 (67.9)	1038 (68.2)
Low intensity	10 (0.7)	1 (0.1)
None	128 (8.4)	134 (8.8)
Ezetimibe	454 (29.8)	421 (27.7)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Patients in the intensive-targeting group had a target low-density lipoprotein (LDL) cholesterol level of less than 55 mg per deciliter, and those in the conventional-targeting group had a target level of less than 70 mg per deciliter. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and IQR interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Patients could have more than one type of atherosclerotic cardiovascular disease.

§ Of the 1474 patients with stable angina, 1443 had evidence of coronary artery disease on coronary angiography or computed tomographic angiography, and 31 had evidence of myocardial ischemia on functional studies without undergoing either imaging procedure.

¶ Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area.

‖ Statin intensity was classified according to the guidelines of the American College of Cardiology and the American Heart Association.[3]

LIPID LEVELS

Serial changes in LDL cholesterol levels are shown in Figure 1A. The median LDL cholesterol level during the trial was 56 mg per deciliter (interquartile range, 48 to 67) (1.4 mmol per liter [interquartile range, 1.2 to 1.7]) in the intensive-targeting group and 66 mg per deciliter (interquartile range, 58 to 76) (1.7 mmol per liter [interquartile range, 1.5 to 2.0]) in the conventional-targeting group, with a consistent between-group difference maintained throughout follow-up. The percentage of patients who reached the assigned target LDL cholesterol level at 1 month was 31.2% in the intensive-targeting group and 59.4% in the conventional-targeting group; at 1, 2, and 3 years, the percentages were 42.9%, 53.3%, and 60.8%, respectively, in the intensive-targeting group and 67.2%, 67.7%, and 68.1% in the conventional-targeting group (Table S4). A post hoc analysis showed that 74.1% of the patients in the intensive-targeting group reached an LDL cholesterol level of less than 70 mg per deciliter (the target for the conventional-targeting group) at 1 month, and 78.5%, 82.6%, and 85.2% did so at 1, 2, and 3 years, respectively. Serial changes in other lipid profiles are presented in Table S5.

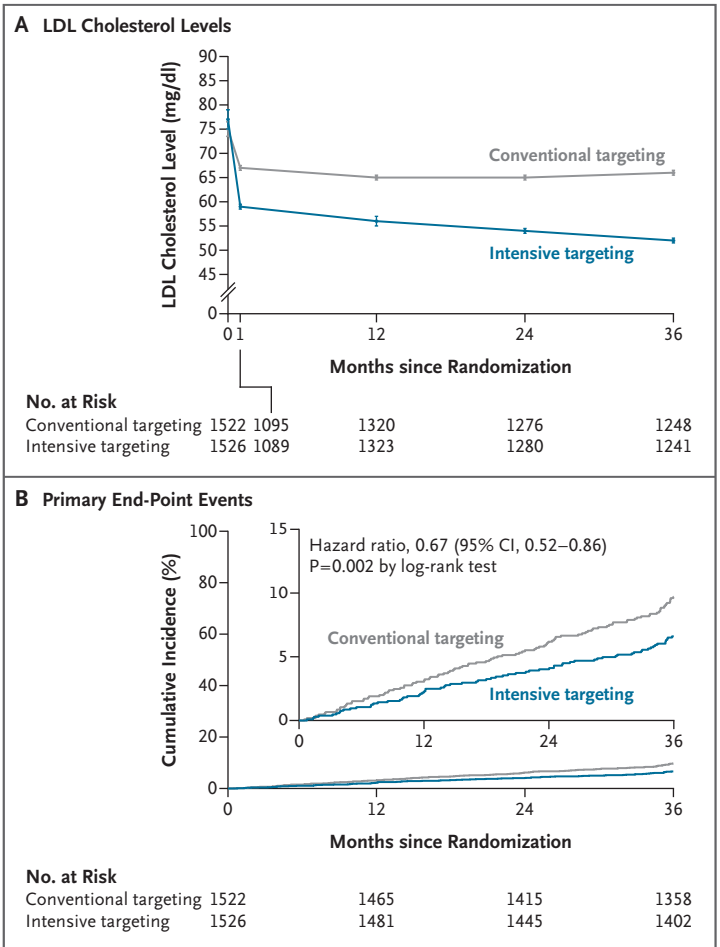

Figure 1. LDL Cholesterol Levels and Primary End-Point Events.

Panel A shows the median levels of low-density lipoprotein (LDL) cholesterol over time in patients assigned to a target LDL cholesterol level of less than 55 mg per deciliter (intensive-targeting group) or less than 70 mg per deciliter (conventional-targeting group). I bars indicate 95% confidence intervals (CIs). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Panel B shows the cumulative incidence of primary end-point events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina) in the two trial groups. The hazard ratio was calculated for the intensive-targeting group relative to the conventional-targeting group. The inset shows the same data on an expanded y axis.

PRIMARY AND SECONDARY END POINTS

During a median follow-up of 3.0 years, a primary end-point event occurred in 100 patients (Kaplan–Meier estimate of cumulative incidence, 6.6%) in the intensive-targeting group and in 147 patients (Kaplan–Meier estimate of cumulative incidence, 9.7%) in the conventional-targeting group (hazard ratio for death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina, 0.67; 95% confidence interval [CI], 0.52 to 0.86; P=0.002) (Table 2 and Fig. 1B). Findings for the primary end point appeared to be consistent in the per-protocol population (Table S6 and Fig. S5).

The cumulative incidence of nonfatal myocardial infarction was 0.8% in the intensive-targeting group and 1.7% in the conventional-targeting group (hazard ratio, 0.46; 95% CI, 0.23 to 0.91). The cumulative incidence of any revascularization was 4.8% and 7.5%, respectively (hazard ratio, 0.63; 95% CI, 0.47 to 0.84). The cumulative incidence of death from cardiovascular causes, nonfatal stroke, and hospitalization for unstable angina, as well as the cumulative incidence of the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke and other composite end-point events, is shown in Table 2. The results of competing-risk analyses for the primary and secondary end points were similar to those of the primary analyses (Table S7). Subgroup analyses for the primary end point are shown in Figure 2.

Table 2. Primary and Secondary End Points.*

End Point	Intensive Targeting (N=1526)	Conventional Targeting (N=1522)	Difference (95% CI)	Hazard Ratio (95% CI)
	no. of patients (%)		*percentage points*	
Primary end point				
Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina	100 (6.6)	147 (9.7)	−3.1 (−5.1 to −1.2)	0.67 (0.52 to 0.86)†
Secondary end points				
Components of the primary end point				
Death from cardiovascular causes	15 (1.0)	18 (1.2)	−0.2 (−0.9 to 0.5)	0.83 (0.42 to 1.65)
Nonfatal myocardial infarction	12 (0.8)	26 (1.7)	−0.9 (−1.7 to −0.1)	0.46 (0.23 to 0.91)
Nonfatal stroke	8 (0.5)	10 (0.7)	−0.1 (−0.7 to 0.4)	0.80 (0.32 to 2.03)
Ischemic stroke	7 (0.5)	7 (0.5)	−0.0 (−0.5 to 0.5)	1.00 (0.35 to 2.85)
Hemorrhagic stroke	1 (0.1)	3 (0.2)	−0.1 (−0.4 to 0.1)	0.33 (0.03 to 3.20)
Any revascularization	72 (4.8)	113 (7.5)	−2.7 (−4.5 to −1.0)	0.63 (0.47 to 0.84)
Percutaneous coronary intervention	67 (4.5)	99 (6.6)	−2.2 (−3.8 to −0.5)	0.67 (0.49 to 0.91)
Coronary-artery bypass grafting	1 (0.1)	7 (0.5)	−0.4 (−0.8 to −0.0)	0.14 (0.02 to 1.15)
Other arterial revascularization	6 (0.4)	9 (0.6)	−0.2 (−0.7 to 0.3)	0.67 (0.24 to 1.87)
Hospitalization for unstable angina	22 (1.5)	36 (2.4)	−0.9 (−1.9 to 0.1)	0.61 (0.36 to 1.03)
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	34 (2.3)	54 (3.6)	−1.3 (−2.5 to −0.1)	0.63 (0.41 to 0.96)
Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or any revascularization	95 (6.3)	141 (9.3)	−3.0 (−5.0 to −1.1)	0.66 (0.51 to 0.86)
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or any revascularization	88 (5.8)	132 (8.7)	−2.9 (−4.8 to −1.1)	0.66 (0.50 to 0.86)
Composite of death from any cause, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina‡	116 (7.6)	157 (10.4)	−2.7 (−4.8 to −0.7)	0.73 (0.57 to 0.92)

* Primary and secondary end points were assessed in the intention-to-treat population, which included all the patients who had undergone randomization. Percentages are cumulative incidences at 3 years calculated with the Kaplan–Meier method; therefore, the percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary end points have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

† P=0.002 by a log-rank test.

‡ Death from any cause occurred in 31 patients (2.0%) in the intensive-targeting group and in 29 patients (1.9%) in the conventional-targeting group.

SAFETY

The incidence of new-onset diabetes, worsening of glycemic control, statin-associated muscle symptoms leading to changes in therapy dose or regimen, cancer diagnosis, cataract surgery, elevation of the aminotransferase level, and elevation of the creatine kinase level did not differ substantially between the two trial groups (Table 3). However, the incidence of elevation of the creatinine level (to >1.5 times the baseline value) was lower in the intensive-targeting group than in the conventional-targeting group (1.2% vs. 2.7%; P=0.004).

DISCUSSION

This trial showed that among patients with atherosclerotic cardiovascular disease, targeting an LDL cholesterol level of less than 55 mg per deciliter (intensive targeting) was associated with a significantly lower 3-year risk of the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina than targeting a level of less than 70 mg per deciliter (conventional targeting). No substantial

between-group differences in the incidence of prespecified safety end-point events were observed, except for an elevation in the serum creatinine level, which occurred less frequently in the intensive-targeting group.

For secondary prevention in patients with atherosclerotic cardiovascular disease, LDL cholesterol–lowering therapy is a cornerstone of management, and previous guidelines for dyslipidemia recommended an LDL cholesterol level of less than 70 mg per deciliter as the initial therapeutic target.[3,4,17] This recommendation was based primarily on data from randomized trials showing that high-intensity statins effectively reduce LDL cholesterol levels and lower cardiovascular risk among patients with atherosclerotic cardiovascular disease.[5-7] Subsequent randomized trials showed that the addition of ezetimibe or PCSK9 inhibitors to statins produced further reductions in LDL cholesterol levels, to less than 55 mg per deciliter, and

Subgroup	Intensive Targeting	Conventional Targeting	Hazard Ratio for Primary End-Point Event (95% CI)
	no. of patients with event/total no. of patients (%)		
Overall	100/1526 (6.6)	147/1522 (9.7)	0.67 (0.52–0.86)
Age			
<65 yr	42/736 (5.7)	70/708 (9.9)	0.56 (0.38–0.83)
≥65 yr	58/790 (7.5)	77/814 (9.5)	0.77 (0.55–1.09)
Sex			
Male	78/1204 (6.5)	129/1206 (10.8)	0.59 (0.45–0.79)
Female	22/322 (7.0)	18/316 (5.7)	1.22 (0.66–2.28)
Body-mass index			
<25	49/779 (6.4)	83/806 (10.4)	0.60 (0.42–0.85)
≥25	51/747 (6.9)	64/716 (9.0)	0.76 (0.53–1.10)
Previous acute coronary syndrome			
Yes	60/827 (7.3)	90/867 (10.5)	0.69 (0.50–0.96)
No	40/699 (5.8)	57/655 (8.8)	0.65 (0.43–0.97)
Coronary or other arterial revascularization			
Yes	66/1015 (6.6)	107/1034 (10.4)	0.62 (0.46–0.84)
No	34/511 (6.7)	40/488 (8.3)	0.80 (0.51–1.27)
Stroke or transient ischemic attack			
Yes	6/57 (10.5)	9/60 (15.3)	0.67 (0.24–1.88)
No	94/1469 (6.5)	138/1462 (9.5)	0.67 (0.52–0.87)
Peripheral artery disease			
Yes	11/132 (8.4)	17/134 (12.9)	0.63 (0.30–1.35)
No	89/1394 (6.5)	130/1388 (9.4)	0.67 (0.52–0.88)
Hypertension			
Yes	85/1136 (7.6)	115/1103 (10.5)	0.71 (0.54–0.94)
No	15/390 (3.9)	32/419 (7.7)	0.50 (0.27–0.92)
Diabetes			
Yes	39/605 (6.5)	72/602 (12.1)	0.53 (0.36–0.78)
No	61/921 (6.7)	75/920 (8.2)	0.81 (0.58–1.13)
Chronic kidney disease			
Yes	13/91 (14.7)	14/87 (16.4)	0.90 (0.42–1.91)
No	87/1435 (6.1)	133/1435 (9.3)	0.64 (0.49–0.84)
LDL cholesterol level at baseline			
<100 mg/dl	73/1184 (6.2)	112/1192 (9.5)	0.65 (0.48–0.87)
≥100 mg/dl	27/342 (8.0)	35/330 (10.7)	0.74 (0.45–1.22)

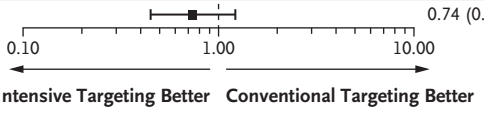

Figure 2. Subgroup Analyses of the Primary End Point.

Shown are hazard ratios (intensive targeting vs. conventional targeting) for primary end-point events across prespecified subgroups. Percentages are cumulative incidences at 3 years calculated with the Kaplan–Meier method; therefore, the percentages may not reflect the ratio of the numerator and the denominator. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 3. Safety End Points*

End Point	Intensive Targeting (N=1526)	Conventional Targeting (N=1522)	Difference (95% CI)	P Value
			percentage points	
New-onset diabetes among patients without diabetes at baseline — no. of patients/total no. (%)	153/921 (16.6)	148/920 (16.1)	0.5 (–2.9 to 3.9)	0.81
Worsening of glycemic control among patients with diabetes at baseline — no. of patients/total no. (%)	295/605 (48.8)	305/602 (50.7)	–1.9 (–7.5 to 3.7)	0.55
Statin-associated muscle symptoms leading to changes in therapy dose or regimen — no. of patients (%)	15 (1.0)	9 (0.6)	0.4 (–0.2 to 1.0)	0.31
Diagnosis of cancer — no. of patients (%)	36 (2.4)	40 (2.6)	–0.3 (–1.4 to 0.8)	0.72
Cataract surgery — no. of patients (%)	20 (1.3)	16 (1.1)	0.3 (–0.5 to 1.0)	0.62
Laboratory abnormalities at any time				
Aminotransferase elevation — no. of patients (%)†	37 (2.4)	23 (1.5)	0.9 (–0.1 to 1.9)	0.09
Creatinine elevation — no. of patients/total no. (%)‡	18/1517 (1.2)	41/1515 (2.7)	–1.5 (–2.5 to –0.5)	0.004
Creatine kinase elevation — no. of patients (%)§	4 (0.3)	4 (0.3)	0.0 (–0.4 to 0.4)	1.00

* Safety end points were assessed in the intention-to-treat population.
† Aminotransferase elevation was defined as a level at least three times the upper limit of the normal range.
‡ Creatinine elevation was defined as a level more than 1.5 times the baseline value. Patients who were undergoing dialysis at the start of the trial were excluded from the analysis.
§ Creatine kinase elevation was defined as a level more than four times the upper limit of the normal range.

improved cardiovascular outcomes.[8-10] On this basis, updated European guidelines introduced a new target of less than 55 mg per deciliter for patients with atherosclerotic cardiovascular disease, a recommendation also supported by the American College of Cardiology expert consensus for patients at very high risk for cardiovascular events.[1,2,18]

However, most previous trials of high-intensity statins, ezetimibe, and PCSK9 inhibitors evaluated primarily the effects of these therapies themselves rather than the strategies defined by specific LDL cholesterol targets.[5-10] The TST (Treat Stroke to Target) trial showed cardiovascular benefit from targeting a lower LDL cholesterol level in patients with ischemic stroke or transient ischemic attack. However, the TST trial compared a target LDL cholesterol level of less than 70 mg per deciliter with a target of 90 to 110 mg per deciliter (2.3 to 2.8 mmol per liter), which does not reflect recent recommendations.[1,2,19] Evidence from randomized trials comparing an LDL cholesterol target of less than 55 mg per deciliter with a target of less than 70 mg per deciliter in patients with atherosclerotic cardiovascular disease has been limited. The present trial addresses this gap in evidence, and the results suggest that intensive targeting confers greater cardiovascular benefit for secondary prevention in patients with atherosclerotic cardiovascular disease than conventional targeting, findings that support the latest guideline recommendations.[1,2]

In addition to the definition of a specific LDL cholesterol target, the approach to achieving the target warrants strategic consideration. In the TST trial, 53% of the patients in the lower-target group (with an LDL cholesterol target of <70 mg per deciliter) reached the target, and only 34% of the patients in this group received ezetimibe.[19] In contrast, in the present trial, the most potent statins (rosuvastatin and atorvastatin) were used, 50.0% of the patients were assigned to receive ezetimibe beginning at randomization, and PCSK9 inhibitors were also permitted. At 3 years, 60.8% of the patients in the intensive-targeting group had an LDL cholesterol level of less than 55 mg per deciliter, and 85.2% had a level of less than 70 mg per deciliter; 48.4% of the patients in the intensive-targeting group were receiving high-intensity statins at 3 years, 66.6% were receiving ezetimibe, and 2.3% were receiving PCSK9 inhibitors. These percentages were substantially higher than those in the conventional-targeting group.

These findings may help explain the cardiovascular benefit of intensive targeting of LDL choles-

terol. Previous trials involving intravascular imaging have shown that intensive LDL cholesterol–lowering therapy with high-intensity statins, ezetimibe, or PCSK9 inhibitors effectively slows atherosclerosis progression and promotes plaque regression.[20-22] However, achieving an LDL cholesterol level of less than 55 mg per deciliter remains challenging, which underscores the need for more aggressive efforts, including earlier and broader use of PCSK9 inhibitors. According to real-world data, the situation is worrisome, with fewer than 25% of patients with atherosclerotic cardiovascular disease reaching an LDL cholesterol level of less than 55 mg per deciliter, fewer than 10% receiving ezetimibe, and approximately 1% receiving PCSK9 inhibitors.[11,12] The present findings support intensifying LDL cholesterol–lowering therapy through the active use of ezetimibe and additional nonstatin agents.[1-3,8-10,12,18,23-26] With the most recent guidelines endorsing a target LDL cholesterol level of less than 40 mg per deciliter for patients at extreme risk, the proactive role of nonstatin agents, including early combination therapy with ezetimibe, warrants further dedicated investigation.[1,18]

Beyond lowering LDL cholesterol and reducing cardiovascular risk, safety remains an important consideration.[1-4] Concerns have been raised about a potential association between high-intensity statins and new-onset diabetes.[27,28] However, further lowering of LDL cholesterol levels with ezetimibe or PCSK9 inhibitors has not been associated with an increased risk of diabetes.[29,30] The present trial showed no substantial between-group differences in the incidence of new-onset diabetes or worsening of glycemic control. In addition, no substantial between-group differences were observed in the incidence of muscle symptoms that led to therapy modification or in the incidence of elevation of aminotransferase or creatine kinase levels. Fewer cases of creatinine elevation occurred in the intensive-targeting group than in the conventional-targeting group. Although data from several studies have suggested that statins are beneficial in mitigating a decline in kidney function, the effects of intensive LDL cholesterol lowering on the progression of kidney disease remain uncertain.[31,32] To further clarify safety, changes in insulin resistance and proteinuria should be addressed in subsequent analyses, and longer follow-up will be required.

Several limitations of the current trial should be noted. First, the trial was unblinded. Blinding was not feasible because the physicians could not make decisions about LDL cholesterol–lowering therapy without knowledge of the assigned LDL cholesterol targets. Nevertheless, members of the event adjudication committee remained unaware of both the trial-group assignments and LDL cholesterol levels, and end-point analyses adhered to precisely defined, prespecified criteria. Second, although the assumption of superiority of intensive targeting to conventional targeting was met for the primary end point, the actual number of primary end-point events was lower than anticipated. Third, despite a gradual increase in the percentage of patients reaching the target LDL cholesterol level in the intensive-targeting group, 39% did not reach the target at 3 years. This outcome may reflect the limited use of PCSK9 inhibitors, which were reserved as the final step after adjustment of the statin dose and addition of ezetimibe — a practice that was constrained by reimbursement policies. In addition, other nonstatin agents, including inclisiran and bempedoic acid, were not used because they were unavailable in South Korea during the trial period; their availability may have enabled more patients in the intensive-targeting group to reach the target level. Fourth, LDL cholesterol levels and other continuous variables were analyzed with the use of available measurements, without imputation, which may have introduced downward bias, with potential underestimation of LDL cholesterol levels. Fifth, the 3-year follow-up period may have been insufficient to fully evaluate the long-term effects of the two LDL cholesterol targets. Sixth, the trial included only East Asian patients. Although previous trials in East Asian populations showed results consistent with the expected effects of LDL cholesterol–lowering therapies, racial or ethnic disparities in cardiovascular risk warrant consideration (Table S8).[24,33]

In the Ez-PAVE trial involving patients with atherosclerotic cardiovascular disease, targeting an LDL cholesterol level of less than 55 mg per deciliter resulted in a lower 3-year risk of the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina than targeting a level of less than 70 mg per deciliter.

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